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Neurocognition and Inhibitory Control in Polysubstance Use Disorders: Comparison with Alcohol Use Disorders and Changes with Abstinence

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Abstract

Introduction—Intact neurocognition and early cognitive recovery during abstinence are important for substance use treatment outcome. Yet, little is known about them in the largest group of treatment seekers today, individuals with polysubstance use disorders (PSU). This study primarily contrasted PSU and individuals with an alcohol use disorder (AUD) on neurocognitive and inhibitory control measures and, secondarily, measured changes during abstinence in PSU.

Method—At one month of abstinence from all substances except tobacco, 36 PSU and 69 AUD completed neurocognitive assessments of executive function, general intelligence, auditory-verbal learning/memory, visuospatial learning/memory/skills, processing speed, working memory, fine motor skills, and cognitive efficiency. The groups were also assessed on inhibitory control measures of self-reported impulsivity, risk-taking, and decision-making. Seventeen PSU repeated the assessments after approximately four months of abstinence. All cross-sectional and longitudinal analyses included smoking status as a possible confound.

Results—At baseline, PSU performed significantly worse than AUD on auditory-verbal memory and on an inhibitory control measure of impulsivity. Polysubstance users showed trends to worse performance than AUD on general intelligence, auditory-verbal learning, and a decision-making task. Between one and four months of abstinence, PSU showed significant improvements on several neurocognitive and inhibitory control measures.

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Conclusions—Polysubstance users exhibit distinct differences in neurocognition and inhibitory control compared to AUD. Between one and four months of abstinence, neurocognition and inhibitory control improve in PSU. This neurocognitive recovery in some domains of abstinent PSU is influenced by smoking status. These results underscore the clinical value of select methods to augment neurocognitive recovery in PSU through appropriate interventions.

Keywords

Cognition; impulsivity; addiction; substance use disorders; longitudinal; recovery

INTRODUCTION

Treatment-seeking individuals with an alcohol use disorder (AUD) exhibit a range of neurocognitive (e.g., (Bates et al., 2002; Bell et al., 2016; Durazzo et al., 2006; Fein et al., 1990; Oscar-Berman et al., 2014; Pennington et al., 2013; Sullivan et al., 2000) and inhibitory control (de Wit, 2009; Naim-Feil et al., 2014; Rupp et al., 2016) deficits. A recent review describes deficits related to working memory, visuospatial functions, inhibition, and executive-based functions such as mental flexibility, problem solving, divided attention (Bernardin et al., 2014), and cognitive control (Wilcox et al., 2014). AUD also exhibit worse cognitive efficiency than controls (Nixon et al., 1998). Of clinical relevance, inhibitory control deficits are greater in actively drinking alcoholics compared to controls (Moody et al., 2015; Vuchinich and Simpson, 1998) and they predict relapse in AUD (Rupp et al., 2016). Research has also noted deleterious effects on neurocognition from chronic cigarette smoking, the most common substance use comorbidity in AUD, with rates in treatment-seeking populations estimated at 60–90% (Durazzo et al., 2007; Hurt et al., 1994; Kalman et al., 2005; Romberger and Grant, 2004). Greater smoking severity in AUD predicted worse executive function (Glass et al., 2009), and smoking AUD performed worse than nonsmoking AUD on domains of auditory-verbal learning and memory, processing speed, cognitive efficiency, and working memory at one week and four weeks of abstinence (Durazzo et al., 2006; Pennington et al., 2013). Furthermore, smoking was shown to significantly hinder recovery of visuospatial learning and processing speed in AUD (Durazzo et al., 2014; Pennington et al., 2013).

A large proportion of treatment-seeking AUD have a concurrent substance use disorder (e.g., cocaine, amphetamines, marijuana, etc.), with 1.3 million people in the United States alone in 2013 (Kedia et al., 2007; Substance Abuse and Mental Health Services Administration, 2013); therefore, this group is better described as “polysubstance users” (PSU), a term used in the literature to describe AUD who meet dependence criteria for additional substances (Abe et al., 2013; Murray et al., 2015; Pennington et al., 2015; Moreno-Lopez et al., 2012). Given the cognitive and inhibitory control deficits observed in AUD studies, it is not surprising that recently detoxified individuals with a substance use dependence diagnosis on any combination of heroin, alcohol, methamphetamine, and/or cannabis also performed worse than controls on several measures of executive function, including working memory, response inhibition, cognitive flexibility, and on inhibitory control measures of decision making (Moreno-Lopez et al., 2012). Individuals with both alcohol and stimulant dependence performed worse than controls on cognitive efficiency (Nixon et al., 1998),

complex attention and memory (Abi-Saab et al., 2005) as well as delayed discounting (Moody et al., 2015). Furthermore, poorer executive function in abstinent abusers of several substances has been related to the amount of cocaine and cannabis consumed (Fernandez-Serrano et al., 2010b), suggesting clinically relevant consequences of chronic substance use.

Despite extensive research into the neurocognitive correlates of substance abuse, only few studies investigated neurocognition in PSU relative to the more extensively studied AUD, and then only on specific tasks. Short-term abstinent alcohol and stimulant dependent individuals performed worse than AUD on immediate and delayed recall conditions of a verbal memory task (Horner, 1997), but they did not differ from AUD on cognitive efficiency tasks of visual perception and category sorting (Nixon et al., 1998). Another study (Fernandez-Serrano et al., 2010a) found treatment-seeking abusers of multiple substances to perform moderately worse than AUD on executive function tasks of verbal fluency, working memory, planning, and multi-tasking.

Neurocognitive functions recover at least partially in AUD during sustained abstinence (e.g., (Bernardin et al., 2014)), and some evidence suggests that additional use of other substances by people with AUD impact neurocognitive recovery negatively (Schulte et al., 2014). Very few longitudinal studies have explicitly investigated changes in neurocognition or inhibitory control in abstinent PSU. In one study, individuals with a combined alcohol and cocaine use disorder demonstrated significant improvements on measures of immediate memory over six months of abstinence (Fein et al., 2002), while another described improvements in verbal short-term memory over three to four months of abstinence from multiple substances (Block et al., 2002).Intact neurocognition and inhibitory control are important for addiction treatment efficacy, retention (Aharonovich et al., 2006; Passetti et al., 2008; Streeter et al., 2008; Bernardin 2014; Wilcox et al 2014), and maintenance of abstinence during treatment (de Wit, 2009; Rupp et al., 2016). Recent evidence has shown an association between better treatment response and longitudinal cognitive recovery in AUD (Bates et al., 2013). Identifying the specific neurocognitive and inhibitory control deficits that differentiate PSU and AUD may provide helpful insights into the specific clinical needs of this understudied (Connor et al., 2014), albeit highly prevalent population of PSU in substance use treatment centers today; such deficits potentially differ from those in the more extensively studied AUD population and therefore may require more tailored treatment approaches to increase treatment effectiveness. Our recent reports of different neurobiological abnormalities in AUD and a subset of the PSU cohort presented here (Abe et al., 2013; Murray et al., 2015) further supports the view that neurocognition may also differ between AUD and PSU populations. Accordingly, the main goals of this study were to determine the degree to which one-month-abstinent PSU and AUD differ on neurocognitive functioning and inhibitory control, and if cigarette smoking affects neurocognition in PSU, similar to what has been reported in AUD. A secondary goal was to explore if PSU exhibit improvements of neurocognitive function and inhibitory control between one and four months of abstinence from all substances except tobacco.

METHOD

Participants

Thirty-six treatment-seeking polysubstance users (PSU; 25 smokers, 11 nonsmokers) and 69 treatment-seeking alcohol users (AUD; 39 smokers, 30 nonsmokers) were recruited from substance abuse treatment programs at the San Francisco VA Medical Center and Kaiser Permanente for two different research projects on alcohol and substance use disorders. Table 1 displays group demographics and relevant substance use characteristics. At baseline, PSU and AUD were abstinent from all substances except tobacco for approximately 29 days. Seventeen PSU (11 smokers, 6 nonsmokers; 16 male, 1 female) were restudied after 128 ± 29 days of sustained abstinence from all substances except tobacco. The 19 PSU not restudied at follow-up either self-reported relapse to any amount of substance use after baseline (including alcohol), were found to have relapse notes in their medical charts, or were lost to follow-up. All participants provided written informed consent according to the Declaration of Helsinki prior to participation. Study procedures were approved by the local Committee on Human Research.

All 105 participants met DSM-IV-TR criteria for an alcohol use disorder. In addition, all 36 PSU met DSM-IV-TR criteria for at least one other substance use disorder: 27 (75%) with cocaine use disorder; 12 (33%) with amphetamine use disorder; 7 (19%) with cannabis use disorder; 5 (14%) with opioid use disorder; 1 (3%) with anxiolytic use disorder; and 1 (3%) with hallucinogen use disorder. Not considering cigarette smoking, nine PSU had two or more substance use disorders in addition to an alcohol use disorder. Specifically, of these nine, five participants met criteria for cocaine, amphetamine, and cannabis use disorder and one also met criteria for opioid and hallucinogen use disorders; two participants met criteria for amphetamine and cannabis use disorder (and one of them also met criteria for opioid use disorder); one participant met criteria for cocaine and opioid use disorders, and another met criteria for opioid and anxiolytic use disorders. Nonsmoking participants smoked fewer than 20 cigarettes in their lifetime, with no cigarette use in the 10 years prior to study and no history of use of other tobacco products. Smoking participants were actively smoking at the time of the baseline assessment and smoked at least 10 cigarettes per day for 5 years or more, with no periods of smoking cessation greater than 1 month in the 5 years prior to enrollment. None of the PSU studied longitudinally changed their smoking status or severity between assessments.

Medical exclusion criteria were a current or past history of intrinsic cerebral tumors, human immunodeficiency virus or acquired immune deficiency syndrome, cerebrovascular accident, aneurysm, insulin dependent diabetes, chronic obstructive pulmonary disease, non-alcohol related seizures, significant exposure to known neurotoxins, demylenating and neurodegenerative diseases, Wernicke-Korsakoff Syndrome, alcohol-induced persisting dementia, and traumatic brain injury resulting in loss of consciousness for more than 15 minutes. Psychiatric exclusion criteria included schizophrenia or other thought disorders, bipolar disorder, dissociative disorders, posttraumatic stress disorder, obsessive compulsive disorder, and panic disorder (with or without agoraphobia), Hepatitis C, type-2 diabetes, hypertension, and unipolar mood disorders, were not exclusionary given their high

prevalence in substance use disorders (Mertens et al., 2003; Mertens et al., 2005; Moss et al., 2010).

Psychiatric/Behavioral Assessment

At baseline (PSU and AUD) and follow-up (PSU only), each participant completed the Structured Clinical Interview for DSM-IV Axis I Disorder Patient Edition, Version 2.0, as well as questionnaires assessing depressive (Beck, 1978) and anxiety symptoms (State-Trait Anxiety Inventory, form Y-1 (state) and Y-2 (trait), STAI, (Spielberger et al., 1977)). Lifetime alcohol consumption was assessed at baseline with the Lifetime Drinking History semi-structured interview (Skinner and Sheu, 1982; Sobell et al., 1988). We derived the average number of standard alcoholic drinks (containing 13.6 g of ethanol) consumed per month, both one year before enrollment and over lifetime. Substance use history of PSU participants was assessed at baseline with a semi-structured interview developed in-house (Pennington et al., 2015). For each substance for which a PSU participant met criteria for a current or past substance use diagnosis, date of last use, frequency of use, and quantity of use (in grams) were gathered. All follow-up PSU maintained abstinence from all substances except tobacco. Abstinence was assessed with self-report, and confirmed via medical chart review, mandating negative urine toxicology and blood alcohol concentration tests conducted weekly as part of routine clinical care. The Fagerstrom Tolerance Test for Nicotine Dependence (Fagerstrom et al., 1991) was used to assess level of nicotine dependence, total years of cigarette smoking, and average number of daily cigarettes currently smoked.

Neurocognitive Assessment

A comprehensive neurocognitive battery was administered to each participant at baseline and again to PSU participants at follow-up. The battery included measures of executive function, general intelligence, auditory-verbal learning/memory, visuospatial learning/memory/skills, processing speed, working memory, cognitive efficiency, and fine motor skills. Neurocognitive domains and constituent measures are presented in Table 2. Alternate forms for Brief Visuospatial Memory Test – Revised (BVMT-R) and California Verbal Learning Test-II (CVLT-II) were used at follow-up assessments for PSU. Premorbid verbal intelligence was estimated with the American National Adult Reading Test at baseline only (AMNART; (Grober and Sliwinski, 1991). All measures are well normed and commonly used in clinical and/or research settings (Strauss et al., 2006). In order to mitigate the potential for nicotine withdrawal effects on cognition, smokers were allowed to smoke *ad libitum* prior to the assessment and were allowed to take cigarette smoking breaks as requested.

Raw scores for neurocognitive measures, except the Luria-Nebraska Item 99 ratio, were converted to age-adjusted (i.e., BVMT-R, CVLT-II, Short Categories Test, Stroop Color–Word Test, Wechsler Adult Intelligence Scale 3rd edition subtests) or age- and education-adjusted (Wisconsin Card Sorting Test-64 variables; Trails A and B, Grooved Pegboard via Heaton Compendium Norms; (Heaton et al., 1991)) standardized scores via the accompanying normative data. Scaled scores and t-scores for all individual neurocognitive tests were transformed to z-scores to ease readability and interpretation of results using a

universal scaled score for neurocognitive measures. Scaled scores were subtracted by 10 (the mean of a scaled score) and divided by 3 (the standard deviation of a scaled score), while t-scores were subtracted by 50 (the mean of a t-score) and divided by 10 (the standard deviation of a t-score). Neurocognitive domain scores are the arithmetic average of z-scores for all associated constituent measures. The cognitive efficiency domain consisted of all tests that were timed, or in which the time to complete the task influence the score achieved. For the Luria-Nebraska Item 99 measure, the number correct (possible range of scores: 0–8) was divided by time required to complete the task. This ratio was used due to the low ceiling for the number of correct responses (i.e., most participants achieved a score of six or better), resulting in a non-Gaussian distribution. Finally, the arithmetic average of z-scores for all individual neurocognitive measures was calculated to form a global neurocognition score for each participant.

Measures of Inhibitory Control (self-reported impulsivity, risk-taking, and decision-making)

Participants completed the Barratt Impulsivity Scale-11 (Patton et al., 1995), a self-report impulsivity questionnaire. The BIS-11 consists of 30 items rated on a scale of “1” (rarely/never) to “4” (almost always) and provides total scores for nonplanning, attentional, motor, and total impulsivity. Participants also completed the Balloon Analogue Risk Task (BART) (Lejuez et al., 2002), a computerized risk-taking task in which participants pump up balloons to earn increasing monetary reward, with the potential for loss if a balloon overinflates and explodes. The BART yields a score for the adjusted number of pumps (i.e., the average number of pumps on all unexploded balloons), with higher scores indicating a higher propensity for risk-taking. Participants also completed the Iowa Gambling Task (IGT), a task of decision-making in which participants choose cards from four decks (two advantageous and two disadvantageous) with the goal of winning as much money as possible. The IGT yields a raw Net Total score for each participant based on his or her selections. Raw scores were converted to the demographically-corrected T scores, with higher T scores indicating better decision-making skills.

Statistical Analyses

All statistical analyses were performed with SPSS version 22 (IBM, 2012). Generalized linear models were used in all analyses, employing maximum likelihood parameter estimation, and followed up by pairwise group comparisons; a chi-square statistic (Wald) and corresponding p-value are generated for each parameter estimate. Three statistical models were tested: (1) primary cross-sectional models compared PSU to AUD at one month of abstinence and included fixed predictors of group (PSU, AUD); (2) secondary cross-sectional models investigated potential smoking effects in PSU and AUD at one month of abstinence and included fixed predictors of group (PSU, AUD), smoking status (Smoker, Nonsmoker) and the interaction term of group-by-smoking status; and (3) longitudinal models explored change in neurocognition within PSU between approximately 29 days (for n = 36 and n = 17 PSU at baseline) and 128 days of abstinence (n = 17 PSU at follow-up); predictors included smoking status (smoker, nonsmoker), time (baseline, follow-up), and the time-by-smoking status interaction term.

Patient characteristics of PSU and AUD at baseline were compared using univariate analysis of covariance for continuous variables and Fisher's exact test for categorical variables. Polysubstance users and AUD differed in education, gender, AMNART, hepatitis C frequency, and proportion of individuals on prescribed psychoactive medication; these variables were entered as covariates in our generalized linear models comparing AUD and PSU at baseline. Potential covariates and interaction terms were trimmed from the final model when not predictive of the outcome variable. The proportion of study participants reporting a family history of alcohol problems was not significantly different between PSU and AUD (83% and 86%, respectively).

We accounted for the multiplicity of measures by correcting alpha levels via a modified Bonferroni procedure (Sankoh et al., 1997). This approach considers the mean correlation between variables and the number of tests in the adjustment of alpha levels. All alpha levels were adjusted for both traditional neurocognitive assessment (11 domains) and BIS-11 (3 domains) and their average inter-correlation coefficients in primary and secondary models (neurocognitive domains: $r = 0.429$, BIS-11: $r = 0.450$) and in tertiary models (neurocognitive domains: $r = 0.358$, BIS-11: $r = 0.495$). The corresponding adjusted alpha levels for primary and secondary models were $p \leq 0.013$ for neurocognitive domains and $p \leq 0.027$ for self-reported impulsivity. The corresponding adjusted alpha levels for tertiary models, which included PSU only, were $p \leq 0.011$ for neurocognitive domains and $p \leq 0.017$ for BIS-11. Alpha levels for risk-taking (BART) and decision-making (IGT) were not adjusted as these are individual tasks measuring separate domains of executive function. Effect sizes (ES) for mean differences between groups (PSU *versus* AUD) were calculated with Cohen's d (Cohen, 1988). We correlated cognitive functioning, risk-taking, decision-making and self-reported impulsivity measures to alcohol use in PSU and AUD, and to cocaine, and marijuana use in PSU only at baseline. Since these were exploratory correlations, we chose a less restrictive alpha level of 0.05.

RESULTS

Characterization of study participants

Of the 36 PSU participants, 21 were African-American (58%), 9 Caucasian (25%), 4 Latino (11%), 1 Native American (3%), and 1 Polynesian/Pacific Islander (3%). Of the 69 AUD participants, 48 were Caucasian (71%), 9 Latino (13%), 7 African-American (10%), 3 Native American (4%), 1 Asian (1%), and 1 declined to disclose ethnicity (1%). The PSU group had a smaller proportions of women (2% vs. 25%), and individuals on prescribed psychoactive medication (25% vs 62%) than AUD. The groups did not differ on mean age at baseline (PSU: 46 years; AUD: 48 years), rate of mood disorder, rate of hypertension, rate of smoking, drinking variables, mean BDI and STAI scores, mean number of days abstinent at baseline, or proportion of family members with alcohol problems. The PSU group started drinking any alcohol at age 14 (the AUD group at age 17), started drinking heavily (i.e., >100 standard alcoholic drinks per month) at age 22 (AUD at age 26), when both groups also started using cocaine, and both groups started smoking cigarettes daily at age 23. The PSU with other substance use disorders started using marijuana at age 16, opioids at age 26 and amphetamines at age 37. See Table 1.

Cross-sectional comparisons of neurocognition and inhibitory control between PSU and AUD

As shown in Table 3, and after co-varying for significant differences in AMNART, PSU performed significantly worse than AUD on auditory-verbal memory [$x^2(1) = 12.16$, $p < 0.001$, ES = 0.72], and PSU exhibited strong trends to worse performance than AUD on intelligence [$x^2(1) = 4.08$, $p = 0.043$, ES = 1.05] and auditory-verbal learning [$x^2(1) = 4.62$, $p = 0.032$, ES = 0.54]. For all other domains except fine motor skills, PSU showed numerically lower scores than AUD with effect sizes up to 0.76 but no statistically significant group differences after covariate correction (where indicated). When smoking status was included as a factor in the cross-sectional group analyses of neurocognitive domains, neither significant group-by-smoking interactions nor main effects of smoking were observed. In addition, gender was not a significant predictor of neurocognitive performance at one month of abstinence, except for fine motor skills which were worse in female than male substance users. Removing the two women from our PSU analyses did not significantly change any of our results.

Polysubstance users exhibited trends to worse decision-making (IGT) than AUD [$x^2(1) = 3.64$, $p = 0.056$, ES = 0.33]; the groups were not significantly different on risk-taking (BART). No significant group-by-smoking interactions or main effects for smoking were observed on either IGT or BART.

Polysubstance users self-reported significantly higher BIS-11 total ($p = 0.002$, ES = 0.36) and nonplanning impulsivity, a measure of cognitive control, than AUD ($p = 0.001$, ES = 0.48), and being on a prescribed psychoactive medication significantly predicted higher total ($p = 0.001$) and nonplanning ($p = 0.005$) impulsivity. With smoking status included in the analyses, no significant group-by-smoking interactions were observed for any of the BIS-11 measures. However, self-reported motor impulsivity showed a trend for a group-by-smoking interaction [$x^2(1) = 3.259$, $p = 0.071$], a significant main effect for group [$x^2(1) = 2.005$, $p = 0.006$], and a trend for a smoking effect [$x^2(1) = 1.499$, $p = 0.066$]. Follow-up pairwise comparisons showed significantly higher motor impulsivity in smoking PSU compared to both smoking ($p = 0.006$) and nonsmoking AUD ($p = 0.030$).

Longitudinal change of neurocognition and inhibitory control in abstinent PSU

Between baseline and follow-up, neurocognitive functions in abstinent PSU improved markedly in the following domains: general intelligence, cognitive efficiency, executive function, working memory, and visuospatial skills (all $p < 0.005$), and weaker improvements were observed for global cognition ($p = 0.016$) and processing speed ($p = 0.051$). Abstinent PSU did not change significantly in the domains of learning and memory (both auditory-verbal and visuospatial) or fine motor skills. Preliminary analyses indicate that the lack of significant changes in the domains of visuospatial memory and fine motor skills were related to significant time-by-smoking status interactions (both $p < 0.001$), where only nonsmokers increased on fine motor skills and only smokers improved on visuospatial memory. The BART scores increased significantly with abstinence ($p < 0.005$), whereas the IGT scores did not change during abstinence. Self-reported total and motor impulsivity (BIS-11) decreased significantly with abstinence (both $p < 0.001$) and the nonplanning score tended to

decrease ($p = 0.028$). The following changes were observed when restricting our longitudinal analysis to only those 17 PSU with baseline and follow-up data: general intelligence, executive function, working memory (all $p < 0.05$), visuospatial skills ($p = 0.054$), global cognition ($p = 0.011$), and processing speed ($p = 0.134$). The 19 PSU not studied longitudinally (shown and presumed to have relapsed) differed from our abstinent PSU restudied on lifetime years of cocaine use (24 vs. 15 years in abstainers, $p = 0.009$). PSU not restudied performed significantly worse at baseline than abstinent PSU on cognitive efficiency, processing speed, and visuospatial learning (all $p < 0.05$). Furthermore, they did not differ significantly on years of education, AMNART, tobacco use severity, and proportions of smokers or family members with problem drinking, or the proportion of individuals taking a prescribed psychoactive medication.

Associations of substance use measures with neurocognition and inhibitory control

In PSU, more lifetime years drinking correlated with worse performance on domains of cognitive efficiency, executive function, intelligence, processing speed, visuospatial skills, and global cognition (all $p < 0.05$, $r > -0.48$). More cocaine consumed per month over lifetime correlated with worse performance on executive function ($p = 0.03$, $r = -0.42$) and greater attentional impulsivity ($p = 0.04$, $r = 0.37$). More marijuana consumed per month over lifetime correlated with worse performance on fine motor skills ($p = 0.04$, $r = -0.73$) and tended to correlate with higher BIS-11 motor impulsivity ($p = 0.09$, $r = 0.64$); in addition, more marijuana use in the year preceding the study correlated with higher nonplanning ($p = 0.03$, $r = 0.77$) and total ($p = 0.07$, $r = 0.66$) impulsivity. Earlier onset age of marijuana use correlated with higher nonplanning impulsivity ($p < 0.01$; $r = -0.88$) and worse visuospatial learning ($p = 0.03$; $r = -0.75$). Interestingly, more lifetime years of amphetamine use correlated with better performance on fine motor skills, executive function, visuospatial skills, and global cognition (all $p < 0.05$, $r < 0.82$).

Similar to the associations found in PSU, more lifetime years drinking in AUD correlated with worse performance on cognitive efficiency, visuospatial skills, and global cognition (all $p \leq 0.05$, $r > -0.40$), and worse performance on visuospatial memory correlated with greater monthly alcohol consumption averaged over the year preceding assessment ($p = 0.01$, $r = 0.31$) and over lifetime ($p = 0.05$, $r = 0.24$). In addition, longer duration of alcohol use in AUD was related to worse auditory-verbal learning and memory (both $p \leq 0.04$, $r \geq -0.28$). Earlier age of onset of heavy drinking in AUD was associated with worse decision-making (IGT) ($p = 0.05$, $r = -0.25$).

DISCUSSION

Our primary aim was to compare neurocognitive functioning and inhibitory control in one-month-abstinent PSU and AUD. Polysubstance users at one month of abstinence showed decrements on a wide range of neurocognitive and inhibitory control measures compared to normed measures. The decrements in neurocognition ranged in magnitude from 0.2 (auditory-verbal learning) to 1.4 (visuospatial learning) standard deviation units below a z-score of zero, with deficits >1 standard deviation below the mean observed for visuospatial memory and visuospatial learning. In comparisons to AUD, PSU performed significantly

worse on measures assessing auditory-verbal memory, and tended to perform worse on measures of auditory-verbal learning and general intelligence. Chronic cigarette smoking status did not significantly moderate cross-sectional neurocognitive group differences at baseline. In addition, PSU exhibited worse decision-making and higher self-reported impulsivity than AUD (the latter driven by higher motor impulsivity particularly in smoking PSU), signaling potentially greater risk of relapse for PSU than AUD (Schulte et al., 2014). Being on a prescribed psychoactive medication related to higher self-reported impulsivity in PSU. For both PSU and AUD, more lifetime years drinking were associated with worse performance on global cognition, cognitive efficiency, general intelligence, and visuospatial skills. Within PSU only, greater substance use quantities related to worse performance on executive function and fine motor skills, as well as to higher self-reported impulsivity.

Neurocognitive deficits in AUD have been described extensively. However, corresponding reports in PSU are rare and very few studies compared PSU to AUD during early abstinence on such a wide range of neurocognitive and inhibitory control measures as administered here (Schulte et al., 2014). To our knowledge, no previous reports have specifically shown PSU to perform worse than AUD on domains of auditory-verbal learning and general intelligence at one month of abstinence. Our studies confirmed previous findings of worse auditory-verbal memory (Horner, 1997) and inhibitory control (Moody et al., 2015) in individuals with a comorbid alcohol and stimulant use disorder compared to those with an AUD, and findings of *no* differences between the groups on measures of cognitive efficiency (Nixon et al., 1998). Some of the cross-sectional neurocognitive and inhibitory control deficits described in this PSU cohort are associated with previously described morphometric abnormalities in primarily prefrontal brain regions of a subsample of this PSU cohort with neuroimaging data (Mon et al., 2014; Pennington et al., 2015). Our neurocognitive findings also further complement studies in subsamples of this PSU cohort that exhibit prefrontal cortical deficits measured by magnetic resonance spectroscopy (Abe et al., 2013) and cortical blood flow (Murray et al., 2015).

Our secondary aim was to explore if PSU demonstrate improvements on neurocognitive functioning and inhibitory control measures between one and four months of abstinence from all substances except tobacco. Polysubstance users showed significant improvements on the majority of cognitive domains assessed here, particularly cognitive efficiency, executive function, working memory, self-reported impulsivity, but an unexpected increase in risk-taking behavior (BART). By contrast, no significant changes were observed for learning and memory domains, which were also worst at baseline, resulting in (residual) deficits in visuospatial learning and visuospatial memory at four months of abstinence of more than 0.9 standard deviation units below a z-score of zero. There were also indications for significant time-by-smoking status interactions for visuospatial memory and fine motor skills, however these analyses have to be interpreted with caution and considered very preliminary, considering the small sample sizes of smoking and nonsmoking PSU at follow-up. Nevertheless, the demonstrations of cognitive recovery in abstinent PSU, and potential effects of smoking status on such recovery, are consistent with our observations of corresponding recovery in abstinent AUD (Durazzo et al., 2007; Durazzo et al., 2014; Pennington et al., 2013). The 19 PSU not studied at follow-up (and confirmed or presumed to have relapsed after baseline) differed significantly from abstinent PSU at baseline on

several important variables: they had more years of cocaine use over lifetime, and performed worse on cognitive efficiency, processing speed, and visuospatial learning. As such, these differences should be tested as potential predictors of relapse in future larger studies.

Several factors limit the generalizability of our findings. Our cross-sectional sample size was modest (due to funding restrictions) and therefore our longitudinal sample of abstinent PSU was small; as not uncommon in clinical samples, about half of our PSU cohort relapsed (or were lost to follow-up) between baseline and follow-up, a rate comparable to what has been reported elsewhere (McLellan et al., 2000). This made us focus our longitudinal results reporting on the main effects of time (independent of the effects of smoking status) and to de-emphasize the reporting of time-by-smoking status interactions. Larger studies are needed to examine the potential effects of smoking status and gender on neurocognitive recovery during abstinence from substances. The study sample was drawn from treatment centers of the Veterans Affairs system in the San Francisco Bay Area and a community-based healthcare provider, and the ethnic breakdown of the study groups was different (with PSU being mostly African American and the AUD group predominantly Caucasian). Therefore, our sample may not be entirely representative of community-based substance use populations in general. Although preliminary, the within subject statistics are meaningful as they are more informative for assessing change over time than larger cross-sectional studies at various durations of abstinence. In addition, premorbid biological factors (e.g., genetic vulnerability to the effects of substance use, pulmonary, and cerebrovascular dysfunction) and other behavioral factors (e.g., diet, nutrition, and exercise) not assessed in this study may have influenced cross-sectional and longitudinal outcome measures. Nonetheless, our study is important and of clinical relevance in that it describes deficits in neurocognition and inhibitory control of detoxified PSU that are different from those in AUD, and that appear to recover during abstinence from substances, potentially as a function of smoking status.

Our cross-sectional and longitudinal findings are valuable for improving current substance use rehabilitation programs. The higher impulsivity and reduced cognitive abilities (including decision making) of PSU compared to AUD, likely the result of long-term comorbid substance use, and the lack of improvements in learning and memory during abstinence indicate a potentially reduced ability of PSU to acquire new cognitive skills necessary for remediating maladaptive behavioral patterns that impede successful recovery. As such, PSU may require a post-detox treatment approach that accounts for these specific deficits relative to AUD. Our results show that PSU able to maintain abstinence for 4 months had less total lifetime years of cocaine use and performed better on cognitive efficiency, processing speed and visuospatial learning than those PSU not restudied (shown and presumed to have relapsed); these variables may therefore be valuable for predicting future abstinence or relapse in PSU. Additionally, and if confirmed in larger studies, our preliminary results on differential neurocognitive change in smoking and nonsmoking PSU may inform a treatment design that addresses the specific needs of these subgroups (i.e., smoking cessation) within this largely understudied population of substance users. Potentially, concurrent treatment of cigarette smoking in treatment-seeking PSU may also help improve long-term substance use outcomes, just as recently proposed for treatment-seeking individuals with AUD (Weinberger et al., 2015). Finally, our findings on neurocognitive improvement in PSU imply that cognitive deficits are to some extent a

consequence of long-term substance use (i.e., state not trait) (Grant and Chamberlain, 2014), which have the potential for remediation with abstinence. This information is of clinical relevance and of psychoeducational value for treatment providers and treatment-seeking PSU alike.

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REFERENCES

Abe C, Mon A, Hoefer ME, Durazzo TC, Pennington DL, Schmidt TP, Meyerhoff DJ. Metabolic abnormalities in lobar and subcortical brain regions of abstinent polysubstance users: magnetic resonance spectroscopic imaging. Alcohol and Alcoholism. 2013; 48:543–551. [PubMed: 23797281]

Abi-Saab D, Beauvais J, Mehm J, Brody M, Gottschalk C, Kosten TR. The effect of alcohol on the neuropsychological functioning of recently abstinent cocaine-dependent subjects. The American Journal on Addictions. 2005; 14:166–178. [PubMed: 16019965]

Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV. Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug and Alcohol Dependence. 2006; 81:313–322. [PubMed: 16171953]

Axelrod BN, Ryan JJ, Ward LC. Evaluation of seven-subtest short forms of the Wechsler Adult Intelligence Scale-III in a referred sample. Archives of Clinical Neuropsychology. 2001; 16:1–8. [PubMed: 14590188]

Bates ME, Bowden SC, Barry D. Neurocognitive impairment associated with alcohol use disorders: implications for treatment. Experimental and Clinical Psychopharmacology. 2002; 10:193–212. [PubMed: 12233981]

Bates ME, Buckman JF, Nguyen TT. A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. Neuropsychology Review. 2013; 23:27–47. [PubMed: 23412885]

Beck, AT. Depression Inventory. Philadelphia: Center for Cognitive Therapy; 1978.

Bell MD, Vissicchio NA, Weinstein AJ. Visual and verbal learning deficits in Veterans with alcohol and substance use disorders. Drug and Alcohol Dependence. 2016; 159:61–65. [PubMed: 26684868]

Benedict, R. Brief Visuospatial Memory Test - Revised: Professional Manual. Odessa, FL: Psychological Assessment Resources, Inc; 1997.

Bernardin F, Maheut-Bosser A, Paille F. Cognitive impairments in alcohol-dependent subjects. Frontiers in psychiatry. 2014; 5:78. [PubMed: 25076914]

Block RI, Erwin WJ, Ghoneim MM. Chronic drug use and cognitive impairments. Pharmacology, Biochemistry and Behavior. 2002; 73:491–504.

Cohen, J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

Connor JP, Gullo MJ, White A, Kelly AB. Polysubstance use: diagnostic challenges, patterns of use and health. Current Opinion in Psychiatry. 2014; 27:269–275. [PubMed: 24852056]

de Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addiction Biology. 2009; 14:22–31. [PubMed: 18855805]

Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test. 2nd. San Antonio, TX: The Psychological Corporation; 2000.

Durazzo TC, Gazdzinski S, Banys P, Meyerhoff DJ. Cigarette smoking exacerbates chronic alcohol-induced brain damage: a preliminary metabolite imaging study. Alcoholism: Clinical and Experimental Research. 2004; 28:1849–1860.

Durazzo TC, Gazdzinski S, Meyerhoff DJ. The neurobiological and neurocognitive consequences of chronic cigarette smoking in alcohol use disorders. Alcohol and Alcoholism. 2007; 42:174–185. [PubMed: 17526627]

Durazzo TC, Pennington DL, Schmidt TP, Meyerhoff DJ. Effects of cigarette smoking history on neurocognitive recovery over 8 months of abstinence in alcohol-dependent individuals. Alcoholism: Clinical and Experimental Research. 2014; 38:2816–2825.

Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. A comparison of neurocognitive function in nonsmoking and chronically smoking short-term abstinent alcoholics. Alcohol. 2006; 39:1–11. [PubMed: 16938624]

Fagerstrom KO, Heatherton TF, Kozlowski LT. Nicotine addiction and its assessment. E Ear Nose and Throat Journal. 1991; 69:763–765.

Fein G, Bachman L, Fisher S, Davenport L. Cognitive impairments in abstinent alcoholics. The Western Journal of Medicine. 1990; 152:531–537. [PubMed: 2190421]

Fein G, Di Sclafani V, Meyerhoff DJ. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. Drug and Alcohol Dependence. 2002; 68:87–93. [PubMed: 12167554]

Fernandez-Serrano MJ, Perez-Garcia M, Perales JC, Verdejo-Garcia A. Prevalence of executive dysfunction in cocaine, heroin and alcohol users enrolled in therapeutic communities. European Journal of Pharmacology. 2010a; 626:104–112. [PubMed: 19836375]

Fernandez-Serrano MJ, Perez-Garcia M, Schmidt Rio-Valle J, Verdejo-Garcia A. Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. Journal of Psychopharmacology. 2010b; 24:1317–1332. [PubMed: 20007413]

Glass JM, Buu A, Adams KM, Nigg JT, Puttler LI, Jester JM, Zucker RA. Effects of alcoholism severity and smoking on executive neurocognitive function. Addiction. 2009; 104:38–48. [PubMed: 19133887]

Golden, CJ. Stroop Color and Word Test. Chicago, IL: Stoelting Company; 1978.

Golden CJ, Hammeke TA, Purisch AD. Diagnostic validity of a standardized neuropsychological battery derived from Luria's neuropsychological tests. Journal of Consulting and Clinical Psychology. 1978; 46:1258–1265. [PubMed: 730876]

Grant JE, Chamberlain SR. Impulsive action and impulsive choice across substance and behavioral addictions: cause or consequence? Addictive Behaviors. 2014; 39:1632–1639. [PubMed: 24864028]

Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. Journal of Clinical and Experimental Neuropsychology. 1991; 13:933–949. [PubMed: 1779032]

Heaton, RK.; Grant, I.; Matthews, CG. Comprehensive norms for an expanded Halstead-Reitan Battery Demographic Corrections, Research Findings, and clinical applications. Odessa, FL: Psychological Assessment Resources, Inc; 1991.

Horner MD. Cognitive functioning in alcoholic patients with and without cocaine dependence. Archives of Clinical Neuropsychology. 1997; 12:667–676. [PubMed: 14590660]

Hurt RD, Eberman KM, Croghan IT, Offord KP, Davis LJ, Morse RM, Bruce BK. Nicotine dependence treatment during inpatient treatment for other addictions: a prospective intervention trial. Alcoholism: Clinical and Experimental Research. 1994; 18:867–872.

IBM. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp; 2012.

Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. American Journal on Addictions. 2005; 14:106–123. [PubMed: 16019961]

Kedia S, Sell MA, Relyea G. Mono- versus polydrug abuse patterns among publicly funded clients. Substance Abuse Treatment, Prevention, and Policy. 2007; 2:33.

Kongs, S.; Thompson, L.; Iverson, G.; Heaton, RK. WCST-64: Wisonsin Card Sorting Test-64 Card Version, Professional Manual. Lutz, FL: Psychological Assessment Resources, Inc; 2000.

Lafayette Instrument, L, IN Grooved Pegboard Test.

Lejuez CW, Read JP, Kahler CW, Richards JB, Ramsey SE, Stuart GL, Brown RA. Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). Journal of Experimental Psychology. 2002; 8:75–84. [PubMed: 12075692]

McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. Journal of the American Medical Association. 2000; 284:1689–1695. [PubMed: 11015800]

Mertens JR, Lu YW, Parthasarathy S, Moore C, Weisner CM. Medical and psychiatric conditions of alcohol and drug treatment patients in an HMO: comparison with matched controls. Archives of Internal Medicine. 2003; 163:2511–2517. [PubMed: 14609789]

Mertens JR, Weisner C, Ray GT, Fireman B, Walsh K. Hazardous drinkers and drug users in HMO primary care: prevalence, medical conditions, and costs. Alcoholism: Clinical and Experimental Research. 2005; 29:989–998.

Mon A, Durazzo TC, Abe C, Gazdzinski S, Pennington D, Schmidt T, Meyerhoff DJ. Structural brain differences in alcohol-dependent individuals with and without comorbid substance dependence. Drug and Alcohol Dependence. 2014; 144:170–177. [PubMed: 25263262]

Moody L, Franck C, Hatz L, Bickel WK. Impulsivity and Polysubstance Use: A Systematic Comparison of Delay Discounting in Mono-, Dual-, and Trisubstance Use. Experimental and Clinical Psychopharmacology. 2015

Moreno-Lopez L, Stamatakis EA, Fernandez-Serrano MJ, Gomez-Rio M, Rodriguez-Fernandez A, Perez-Garcia M, Verdejo-Garcia A. Neural correlates of hot and cold executive functions in polysubstance addiction: association between neuropsychological performance and resting brain metabolism as measured by positron emission tomography. Psychiatry Research. 2012; 203:214–221. [PubMed: 22959812]

Moss HB, Chen CM, Yi HY. Prospective follow-up of empirically derived Alcohol Dependence subtypes in wave 2 of the National Epidemiologic Survey on Alcohol And Related Conditions (NESARC): recovery status, alcohol use disorders and diagnostic criteria, alcohol consumption behavior, health status, and treatment seeking. Alcoholism: Clinical and Experimental Research. 2010; 34:1073–1083.

Murray DE, Durazzo TC, Mon A, Schmidt TP, Meyerhoff DJ. Brain perfusion in polysubstance users: relationship to substance and tobacco use, cognition, and self-regulation. Drug and Alcohol Dependence. 2015; 150:120–128. [PubMed: 25772434]

Naim-Feil J, Fitzgerald PB, Bradshaw JL, Lubman DI, Sheppard D. Neurocognitive deficits, craving, and abstinence among alcohol-dependent individuals following detoxification. Archives of Clinical Neuropsychology. 2014; 29:26–37. [PubMed: 24334264]

Nixon SJ, Paul R, Phillips M. Cognitive efficiency in alcoholics and polysubstance abusers. Alcoholism: Clinical and Experimental Research. 1998; 22:1414–1420.

Oscar-Berman M, Valmas MM, Sawyer KS, Ruiz SM, Luhar RB, Gravitz ZR. Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. Handbook of clinical neurology. 2014; 125:183–210. [PubMed: 25307576]

Passetti F, Clark L, Mehta MA, Joyce E, King M. Neuropsychological predictors of clinical outcome in opiate addiction. Drug and Alcohol Dependence. 2008; 94:82–91. [PubMed: 18063322]

Patton J, Stanford M, Barratt E. Factor structure of the Barratt Impulsiveness Scale. Journal of Clinical Psychology. 1995; 51:768–774. [PubMed: 8778124]

Pennington DL, Durazzo TC, Schmidt TP, Abe C, Mon A, Meyerhoff DJ. Alcohol use disorder with and without stimulant use: brain morphometry and its associations with cigarette smoking, cognition, and inhibitory control. Public Library of Science ONE. 2015; 10:e0122505. [PubMed: 25803861]

Pennington DL, Durazzo TC, Schmidt TP, Mon A, Abe C, Meyerhoff DJ. The effects of chronic cigarette smoking on cognitive recovery during early abstinence from alcohol. Alcoholism: Clinical and Experimental Research. 2013; 37:1220–1227.

Reitan, RM.; Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Interpetation. Tucson, AZ: Neuropsychological Press; 1985.

Romberger DJ, Grant K. Alcohol consumption and smoking status: the role of smoking cessation. Biomedicine and Pharmacotherapy. 2004; 58:77–83. [PubMed: 14992787]

Rupp CI, Beck JK, Heinz A, Kemmler G, Manz S, Tempel K, Fleischhaker WW. Impulsivity and Alcohol Dependence Treatment Completion: Is There a Neurocognitive Risk Factor at Treatment Entry? Alcoholism: Clinical and Experimental Research. 2016; 40:152–160.

Sankoh AJ, Huque MF, Dubey SD. Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Statistics in Medicine. 1997; 16:2529–2542. [PubMed: 9403954]

Schulte MH, Cousijn J, den Uyl TE, Goudriaan AE, van den Brink W, Veltman DJ, Wiers RW. Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. Clinical Psychology Review. 2014; 34:531–550. [PubMed: 25240109]

Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. Journal of Studies on Alcohol and Drugs. 1982; 43:1157–1170.

Sobell L, Sobell M, Leo G, Cancilla A. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. Addiction. 1988; 83:393–402.

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Self-Evaluation Questionaire. 1977

Strauss, E.; Sherman, EMS.; Spreen, O. A Compendium of Neuropsychological Tests: Administration, Norms and Commentary. New York, NY: Oxford University Press; 2006.

Streeter CC, Terhune DB, Whitfield TH, Gruder S, Sarid-Segal O, Silveri MM, Yurgelun-Todd DA. Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. Neuropsychopharmacology. 2008; 33:827–836. [PubMed: 17568399]

Substance Abuse and Mental Health Services Administration, RftNSoDUaH. Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013. NSDUH Series H-48, HHS Publication No (SMA) 14-4863 2014

Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Pattern of motor and cognitive deficits in detoxified alcoholic men. Alcoholism: Clinical and Experimental Research. 2000; 24:611–621.

Vuchinich RE, Simpson CA. Hyperbolic temporal discounting in social drinkers and problem drinkers. Experimental and Clinical Psychopharmacology. 1998; 6:292–305. [PubMed: 9725113]

Wechsler, D. Wechsler Memory Scale - III (WMS - III). San Antonio, TX: The Psychological Corporation; 1997.

Weinberger AH, Platt J, Jiang B, Goodwin RD. Cigarette Smoking and Risk of Alcohol Use Relapse Among Adults in Recovery from Alcohol Use Disorders. Alcoholism: Clinical and Experimental Research. 2015; 39:1989–1996.

Wetzel, L.; Boll, TJ. Short Category Test, Booklet Format. Los Angeles: Western Psychological Services; 1987.

Wilcox CE, Dekonenko CJ, Mayer AR, Bogenschutz MP, Turner JA. Cognitive control in alcohol use disorder: deficits and clinical relevance. Reviews in Neuroscience. 2014; 25:1–24.

Table 1

Demographics, clinical, and substance use variables for PSU and AUD groups at baseline (mean ± standard deviation)

	PSU	AUD
Number of participants	36	69
Race/Ethnicity n (%)		
African American	21 (58)	7 (10)
Asian	0 (0)	1 (1)
Caucasian	9 (25)	48 (71)
Latino	4 (11)	9 (13)
Native Amer./Aleutian	1 (3)	3 (4)
Polynesian/Pac. Island	1 (3)	0 (0)
Other	0 (0)	1 (1)
Gender m (f)	34 (2) *	52 (17) *
Hypertension n (%)	7 (19)	19 (28)
Hepatitis C+ n (%)	7 (19) *	4 (6) *
Being on prescribed psychoactive medication n (%)	9 (25) *	43 (62) *
Mood disorder n (%)	7 (19)	17 (25)
Substance-induced mood disorder n (%)	3 (8)	6 (9)
FH of alcohol problems n (%)	30 (83)	59 (86)
Smoking status n (%)	25 (69) smokers; 11 (31) nonsmokers	39 (57) smokers; 30 (43) nonsmokers
AMNART	105.3 ± 9.1 *	115.3 ± 9.1 *
Education (years)	12.6 ± 1.3 *	14.5 ± 2.3 *
Age at baseline (years)	46.3 ± 10.1	47.8 ± 10.8
BDI	11.2 ± 7.9	12.3 ± 8.3
STAI (State)	34.6 ± 11.0	35.2 ± 11.3
STAI (Trait)	34.8 ± 11.0	35.0 ± 11.2
FTND total	4.4 ± 1.4	4.0 ± 1.6
FTND lifetime highest	15.6 ± 6.5	16.7 ± 8.1
FTND years daily smoking	23.2 ± 12.6	25.3 ± 10.3
1 year average drinks/month	233 ± 232	302 ± 173
Lifetime average drinks/month	211 ± 191	182 ± 108
Lifetime years drinking	31.2 ± 9.9	30.8 ± 11.1
Years heavy drinking[a]	19.2 ± 10.7	18.5 ± 10.7
Onset heavy drinking[a] (age)	22.1 ± 8.9	25.5 ± 8.8
Abstinent from alcohol at baseline (days)	29.8 ± 8.4	28.8 ± 9.7
Years cocaine use (n=27)	18.4 ± 10.6	n/a

	PSU	AUD
Onset cocaine use (age)	22.0 ± 7.8	n/a
Years amphetamine use (n=12)	12.8 ± 8.1	n/a
Onset amphetamine use (age)	37.3 ± 11.8	n/a
Years marijuana use (n=7)	26.9 ± 13.4	n/a
Onset marijuana use (age)	15.6 ± 7.5	n/a
Years opioid use (n=5)	6.3 ± 5.1	n/a
Onset opioid use (age)	26.2 ± 13.7	n/a

[*] significantly different at $p \leq 0.05$

[a] heavy drinking defined as >100 alcoholic drinks/month in men and >80 alcoholic drinks/month in women

AMNART, American National Adult Reading Test; FTND, Fagerstrom Tolerance Test for Nicotine Dependence; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; FH, family history

Table 2

Neurocognitive domains and their constituent measures

Neurocognitive Domain	Constituent Measures
Executive functions	• Short Categories Test (Wetzel and Boll, 1987) • Stroop Test, color-word subtest (Golden, 1978) • Trail Making Test B (Reitan and Wolfson, 1985) • Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) Similarities (Wechsler, 1997) • Wisconsin Card Sorting Test-64 (WCST-64): Computer Version 2-Research Edition non-perseverative errors, perseverative errors, perseverative responses (Kongs et al., 2000)
General intelligence	• Ward-7 Full Scale IQ (Axelrod et al., 2001), based on the following WAIS-III subtests: Arithmetic, Block Design, Digit Span, Digit Symbol, Information Picture Completion
Auditory-verbal learning	• California Verbal Learning Test-II (CVLT-II) Immediate Recall trials 1–5 (Delis et al., 2000)
Auditory-verbal memory	• CVLT-II Short and Long Delay Free Recall (Delis et al., 2000)
Visuospatial learning	• Brief Visuospatial Memory Test-Revised (BVMT-R) Total Recall on learning trials 1–3 (Benedict, 1997)
Visuospatial memory	• BVMT-R Delayed Recall (Benedict, 1997)
Visuospatial skills	• WAIS-III Block Design (Wechsler, 1997) • Luria-Nebraska Item 99 (Golden et al., 1978)
Processing speed	• WAIS-III Digit Symbol (Wechsler, 1997) • WAIS-III Symbol Search (Wechsler, 1997) • Stroop, color-word subtests (Golden, 1978) • Trail Making Test A (Reitan and Wolfson, 1985)
Working memory	• WAIS-III Arithmetic (Wechsler, 1997) • WAIS-III Digit Span (Wechsler, 1997)
Fine motor dexterity	• Grooved Pegboard Test (Lafayette Instrument)
Cognitive efficiency	• This domain consisted of all tests that were timed, or where the time to complete the task influenced the score obtained: – Luria-Nebraska Item 99 (Golden et al., 1978) – Stroop word, color, and color-word tests (Golden, 1978) – Trail Making Test A and B (Reitan and Wolfson, 1985) – WAIS-III Arithmetic, Block Design, Digit Symbol, Picture Completion, and Symbol Search (Wechsler, 1997)

Neurocognitive domains are the arithmetic averages of the z-scores for all constituent measures

Table 3

Measures for neurocognitive domains (Z-scores) and inhibitory control (raw mean ± standard deviation) in PSU and AUD groups at baseline

Neurocognitive Domain/Measure	PSU n = 36	AUD n = 69	Effect size[#]
Global Cognition[$]	−0.58 ± 0.53	−0.12 ± 0.68	0.76
AV learning[$]	−0.23 ± 0.95	0.28 ± 0.94	0.54[*]
AV memory[$]	−0.43 ± 0.95	0.25 ± 0.93	0.72[**]
Cognitive efficiency	−0.44 ± 0.59	−0.06 ± 0.67	0.60
Executive function[$]	−0.36 ± 0.67	−0.16 ± 0.64	0.31
Fine motor skills[$$]	−0.68 ± 0.98	−0.69 ± 1.16	0.01
Intelligence[$]	−0.57 ± 0.71	0.26 ± 0.87	1.05[*]
Processing Speed[$]	−0.41 ± 0.62	−0.09 ± 0.67	0.50
VS memory[$]	−1.10 ± 1.05	−0.89 ± 1.27	0.18
VS skills[$]	−0.59 ± 0.88	−0.14 ± 1.02	0.47
VS learning[$]	−1.35 ± 1.18	−0.89 ± 1.31	0.37
Working memory[$]	−0.47 ± 0.79	0.11 ± 0.82	0.72
BIS-11 total impulsivity[$$$]	68.22 ± 10.5	64.52 ± 10.3	0.36[**]
BIS-11 nonplanning[$$$]	27.6 ± 4.1	25.4 ± 5.0	0.48[**]
BIS-11 attentional[$$$]	16.8 ± 4.2	16.6 ± 4.3	0.05
BIS-11 motor[$$$]	23.8 ± 4.7	22.6 ± 3.8	0.29
IGT (total T-score)[$$$$]	46.6 ± 7.1	49.3 ± 9.5	0.33[*]
BART (adjusted pumps)	584 ± 227	612 ± 215	0.13

[*] PSU show trends to worse performance than AUD after covariate correction

[**] PSU perform significantly worse than AUD after covariate correction adjusted alpha: neurocognitive domains ($p \leq 0.013$); BIS-11 ($p \leq 0.027$); IGT and BART ($p = 0.05$)

[#] Cohen's *d* before covariate correction (weak ≤ 0.30; moderate = 0.31–0.50; strong ≥ 0.51)

[$] AMNART;

[$$] gender;

[$$$] psychoactive medication;

[$$$$] Hepatitis C+;: significant covariate used in group comparison

AV: auditory-verbal; VS: visuospatial; BIS-11: Barratt Impulsivity Scale; IGT: Iowa Gambling Task; BART: Balloon Analogue Risk Task